

# Coexistence of MACC1 and NM23-H1 dysregulation and tumor budding promise early prognostic evidence for recurrence risk of early-stage colon cancer

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## Abstract

© 2017 APMIS. Published by John Wiley & Sons Ltd The tumor-node-metastasis (TNM) classification, the presence of a mucinous component, and signet ring cells are well-known criteria for identifying patients at a high risk for recurrence and determining the therapeutic approach for early-stage colon cancer (eCC). Nevertheless, recurrence can unexpectedly occur in some eCC cases after surgical resection. The aims of the present study were to evaluate the relation of dysregulated MACC1, c-MET, and NM23-H1 expression with the histopathological features of tumors in recurrence formation in eCC cases. A total of 100 sporadic eCC patients without poor prognosis factors were evaluated in this study. The relationship between the altered expression of MACC1, c-MET, and NM23-H1 and pathological microenvironmental features, including the presence of tumor budding and desmoplasia, were assessed. The primary outcomes, including 5-year overall survival (OS) and disease-free survival (DFS), were also measured. Compared with nonrecurrent patients, the expression level of MACC1 was 8.27-fold higher, and NM23-H1 was 11.36-fold lower in patients with recurrence during the 5-year follow-up ( $p = 0.0345$  and  $p = 0.0301$ , respectively). In addition, the coexistence of high MACC1 and low NM23-H1 expression and tumor budding was associated with short OS ( $p < 0.001$ ). We suggest that the combination of reduced NM23-H1, induced MACC1, and the presence of tumor budding are promising biomarkers for the prediction of recurrence and may aid the stratification of patients with stage II colon cancer for adjuvant chemotherapy.

<http://dx.doi.org/10.1111/apm.12801>

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## Keywords

colon cancer, early stage, metastasis-associated colon cancer-1, NME/NM23 nucleoside diphosphate kinase 1, tumor budding

## References

- [1] American Cancer Society. <http://www.cancer.org> -Cancer Facts & Figures, 2008, Atlanta p4., 2008.
- [2] Liu CC, Cai DL, Sun F, Wu ZH, Yue B, Zhao SL, et al. FERMT1 mediates epithelial-mesenchymal transition to promote colon cancer metastasis via modulation of  $\beta$ -catenin transcriptional activity. *Oncogene* 2016;36:1-14.
- [3] Wolpin BM, Mayer RJ. Systemic treatment of colorectal cancer. *Gastroenterology* 2008;134:1296-310.
- [4] Sleeman JP, Thiery JP. SnapShot: the epithelial-mesenchymal transition. *Cell* 2011;145:162.

- [5] Calon A, Espinet E, Palomo-Ponce S, Tauriello DV, Iglesias M, Céspedes MV, et al. Dependency of colorectal cancer on a TGF- $\beta$ -driven program in stromal cells for metastasis initiation. *Cancer Cell* 2012;22:571-84.
- [6] Van Cutsem E, Costa F. Progress in the adjuvant treatment of colon cancer: has it influenced clinical practice? *JAMA* 2005;294:2758-60.
- [7] O'Connell MJ. Oxaliplatin or irinotecan as adjuvant therapy for colon cancer: the results are in. *J Clin Oncol* 2009;27:3082-4.
- [8] Stein U, Walther W, Arlt F, Schwabe H, Smith J, Fichtner I, et al. MACC1, a newly identified key regulator of HGF-MET signaling, predicts colon cancer metastasis. *Nat Med* 2009;15:59-67.
- [9] Stein U, Dahlmann M, Walther W. MACC1 - more than metastasis? Facts and predictions about a novel gene. *J Mol Med* 2010;88:11-8.
- [10] Lee HY, Lee H. Inhibitory activity of nm23-H1 on invasion and colonization of human prostate carcinoma cells is not mediated by its NDP kinase activity. *Cancer Lett* 1999;145:93-9.
- [11] Suzuki E, Ota T, Tsukuda K, Okita A, Matsuoka K, Murakami M, et al. nm23-H1 reduces in vitro cell migration and the liver metastatic potential of colon cancer cells by regulating myosin light chain phosphorylation. *Int J Cancer* 2004;108:207-11.
- [12] Stein U, Smith J, Walther W, Arlt F. MACC1 controls Met: what a difference an Sp1 site makes. *Cell Cycle* 2009;8:2467-9.
- [13] Shirahata A, Shinmura K, Kitamura Y, Sakuraba K, Yokomizo K, Goto T, et al. MACC1 as a marker for advanced colorectal carcinoma. *Anticancer Res* 2010;30:2689-92.
- [14] Haut M, Steeg P, Willson JKW, Markowitz S. Induction of nm23 gene expression in human colonic neoplasm and equal expression in colon tumors of high and low metastatic potential. *J Natl Cancer Inst* 1991;83:712-6.
- [15] Royds JA, Cross SS, Silcocks PB, Scholefield JH, Rees RC, Stephenson TJ. Nm23 antimetastatic gene product expression in colorectal carcinoma. *J Pathol* 1994;172:261-6.
- [16] Jayasinghe C, Simiantonaki N, Kirkpatrick CJ. Histopathological features predict metastatic potential in locally advanced colon carcinomas. *BMC Cancer* 2015;21:14.
- [17] Dawson H, Lugli A. Molecular and pathogenetic aspects of tumor budding in colorectal cancer. *Front Med (Lausanne)* 2015;10:11.
- [18] Chaffer CL, Weinberg RA. A perspective on cancer cell metastasis. *Science* 2011;331:1559-64.
- [19] Eckert MA, Lwin TM, Chang AT, Kim J, Danis E, Ohno-Machado L, et al. Twist1-induced invadopodia formation promotes tumor metastasis. *Cancer Cell* 2011;19:372-86.
- [20] Wang L, Wu Y, Lin L, Liu P, Huang H, Liao W, et al. Metastasis-associated in colon cancer-1 upregulation predicts a poor prognosis of gastric cancer, and promotes tumor cell proliferation and invasion. *Int J Cancer* 2013;15:1419-30.
- [21] Freire-de-Lima L, Gelfenbeyn K, Ding Y, Mandel U, Clausen H, Handa K, et al. Involvement of O-glycosylation defining oncofetal fibronectin in epithelial-mesenchymal transition process. *Proc Natl Acad Sci USA* 2011;108:17690-5.
- [22] Kenny HA, Kaur S, Coussens LM, Lengyel E. The initial steps of ovarian cancer cell metastasis are mediated by MMP-2 cleavage of vitronectin and fibronectin. *J Clin Invest* 2008;118:1367-79.
- [23] Bergers G, Brekken R, McMahon G, Vu TH, Itoh T, Tamaki K, et al. Matrix metalloproteinase-9 triggers the angiogenic switch during carcinogenesis. *Nat Cell Biol* 2000;2:737-44.
- [24] Schoumacher M, Goldman RD, Louvard D, Vignjevic DM. Actin, microtubules, and vimentin intermediate filaments cooperate for elongation of invadopodia. *J Cell Biol* 2010;189:541-56.
- [25] Kapitanović S, Cacev T, Berković M, Popović-Hadžija M, Radosević S, Seiwert S, et al. nm23-H1 expression and loss of heterozygosity in colon adenocarcinoma. *J Clin Pathol* 2004;57:1312-8.
- [26] Di Renzo MF, Olivero M, Giacomini A, Porte H, Chastre E, Mirossay L, et al. Overexpression and amplification of the met/HGF receptor gene during the progression of colorectal cancer. *Clin Cancer Res* 1995;1:147-54.
- [27] Suzuki E, Ota T, Tsukuda K, Okita A, Matsuoka K, Murakami M, et al. nm23-H1 reduces in vitro cell migration and the liver metastatic potential of colon cancer cells by regulating myosin light chain phosphorylation. *Int J Cancer* 2004;108:207-11.
- [28] Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition. *J Clin Invest* 2009;119:1420-8.
- [29] Lochhead P, Kuchiba A, Imamura Y, Liao X, Yamauchi M, Nishihara R, et al. Microsatellite instability and BRAF mutation testing in colorectal cancer prognostication. *J Natl Cancer Inst* 2013;105:11516.
- [30] Brier B, Moses HL. TGF-beta and cancer. *Cytokine Growth Factor Rev* 2006;17:29-40.
- [31] Seong HA, Jung H, Ha H. NM23-H1 tumor suppressor physically interacts with serine-threonine kinase receptor associated protein, a transforming growth factor-beta (TGF-beta) receptor-interacting protein, and negatively regulates TGF-beta signaling. *J Biol Chem* 2007;282:12075-96.
- [32] Zhao R, Gong L, Li L, Guo L, Zhu D, Wu Z, et al. nm23-H1 is a negative regulator of TGF- $\beta$ 1-dependent induction of epithelial-mesenchymal transition. *Exp Cell Res* 2013;10:740-9.

- [33] Messinetti S, Giacomelli L, Fabrizio G, Giarnieri E, Gabatel R, Manno A, et al. Vecchione A. CD44v6 and Nm23-H1 protein expression related to clinicopathological parameters in colorectal cancer. *Ann Ital Chir* 2003;74:45-51.
- [34] Koelzer VH, Zlobec I, Lugli A. Tumor budding in colorectal cancer-ready for diagnostic practice? *Hum Pathol* 2016;47:4-19.
- [35] Kidd ME, Shumaker DK, Ridge KM. The role of vimentin intermediate filaments in the progression of lung cancer. *Am J Respir Cell Mol Biol* 2014;50:1-6.
- [36] Ding Y, Li X, Hong D, Jiang L, He Y, Fang H. Silence of MACC1 decreases cell migration and invasion in human malignant melanoma through inhibiting the EMT. *Biosci Trends* 2016;10:258-64.
- [37] Miyazono K. Transforming growth factor-beta signaling in epithelial-mesenchymal transition and progression of cancer. *Proc Jpn Acad Ser B Phys Biol Sci* 2009;85:314-23.
- [38] Zhao R, Gong L, Li L, Guo L, Zhu D, Wu Z, et al. nm23-H1 is a negative regulator of TGF- $\beta$ 1-dependent induction of epithelial-mesenchymal transition. *Exp Cell Res* 2013;10:740-9.